REMARKS

In response to the Office Action mailed June 26, 2008, Claims 1-4 stand pending. Claims 1-4 have been amended and Claims 5-6 are new. Support for the amended and newly presented claims may be found throughout the specification and more particularly on pages 2-4 and 6-7 inclusive of the specification and the originally filed claims. No new matter has been added.

Claim Rejections

I. 35 USC § 112, 2nd Paragraph

Claims 1-4 stand rejected under 35 USC § 112, 2nd Paragraph for alleged indefiniteness regarding location of the CGT codon in the claimed sequence. Applicants respectfully traverse and overcome this rejection.

Applicants have amended Claims 1-4 to recite SEQ ID NO: 3 as the claimed sequence and thus the claimed location(s) of the CGT codon. SEQ ID NO: 3 comprises as first encoded amino acid a thionine, which is not part of the amino acid sequence of HGF. Thus, the amino acid sequence starts with amino acid number 2 of SEQ ID NO:3 which corresponds to amino acid number 32 of HGF containing the signal peptide. Therefore, the numbered codons 33, 35 and 36, (originally claimed) respectively, encode the amino acids 3, 5 and 6 of SEQ ID NO:3 (as now claimed).

Accordingly, Applicants respectfully submit that Claims 1-4, as now amended, clearly recite the location of the CGT codon at specified location(s) and as such that Claims 1-4 are now definite. Therefore, Applicants respectfully request that the 112, 2nd paragraph rejection be withdrawn and Claims 1-4 be placed into condition for allowance.

II. 35 USC § 103(a)

Claims 1-4 stand rejected under 35 USC § 103(a) for alleged obviousness over Stahl et al in view of three additional references, Fuglsang, Olivares-Trejo et al. and Jeh et al. Applicants respectfully traverse and overcome this rejection.

The Examiner contends that basically Stahl discloses recombinant human hepatocyte growth factor isoforms produced in E. coli, but acknowledges Stahl's failure to disclose substitution of a CGT codon at positions 33, 35 and 36 of NK1/NK2. The Examiner alleges that Fuglsang discloses CGT as the most optimal codon for Arg, that Olivares-Trejo discloses increase of a different protein in E.coli when arginine codons AGA and AGG in said different protein are changed to CGT and that finally Jeh discloses that in the production of yet another different protein (fGH) in E.coli, that changing the first 15 codons of fGH with other codons, including CGT for Arg, resulted in better production of this yet another different protein. Applicants respectfully traverse and overcome this rejection.

First, Applicants respectfully point out that the Examiner at best has only shown results involving different proteins. Olivares-Trejo is directed to the expression of the int gene and is completely silent about HGF. Jeh is also directed to the expression of a different protein and involves many different and multiple simultaneous codon changes as being related to better expression. Applicants respectfully submit that neither Olivares-Trejo nor Jeh are relevant art to the instant application.

Second, Applicants note that Claims 1-4 are directed to SEQ ID NO: 3. This sequence contains as first encode amino acid a methione, which is not part of the amino acid sequence of HGF. There is no indication, no teaching and no suggestion in any of the cited references, singularly or taken together, of using or encoding SEQ ID NO: 3. Accordingly, Applicants respectfully submit that the cited references citing

different sequences and/or completely different proteins do not render Applicants claimed invention regarding SEQ ID NO;3 obvious.

Third, Applicants respectfully submit that the cited references actually do not teach nor disclose the Examiner's suggested interpretation. For example, Fuglsang et al is directed to "the effective number of codons for individual amino acids". The codon usage of Arg is not discussed in this document. Only in Table 2 on page 188 the correlation between the RSCU value and the Nc(AA) or CAI value, respectively is given. Further it is outlined on page 187, right column, end of the column, that "Table:2 list the correlation coefficient for all codons belonging to the amino acids under investigation in this study, and it can be seen that when a significant and negative correlation is observed, then the codon is optimal, but an optimal codon does not necessarily show negative correlation" (emphasis added). On page 189, left column, it is outlined that "that optimality is not a phenomenon that is confined solely to expressivity, but that other factors might render a codon optimal under certain conditions" (emphasis added). Additionally, the complete document is silent about the optimal codon for the amino acid Arg, and in table 2 two codons are listed which may be used as optimal codons (emphasis added).

Thus, Fuglsang et al does not provide a hint towards an optimal codon for the amino acid Arg and, furthermore, it qualifies its own findings by admitting, that other factors beside the codon may render a codon optimal. Therefore, a person skilled in the art would not take the teach of Fuglsang et al as to favor a specific codon but only that there may exist a codon that is preferred in comparison to their codons.

Moreover, as noted above, Olivares-Trejo et al is directed to the expression of the int gene. Most importantly, Olivares-Trejo et al is completely silent about HGF and is also completely silent about high yield production. Further, Olivares-Trejo et al reports that "cell growth and int protein synthesis were enhanced by overexpression of Pth and $tRNA^{Arg4}$ cognate to AGG and AGA but not of $tRNA^{Ile2a}$ specific for ATA. The increase of

int protein synthesis also takes place when the rate arginine codons AGA and AGG at positions 3 and 4 are changed to common arginine CG% or lysine AAA codons but not to rate isoleucine ATA codons".

Thus, Olivares-Trejo et al provides for at least three alternatives, i.e. expression of the tRNA required for the codon or change of the codons to codons encoding the same amino acid or change of the codons to codons encoding lysine. Furthermore, all this has only been exemplified for the int protein. Therefore, a person skilled in the art would not be motivated to take the teaching of Olivares-Trejo et al into account when looking for a method related to a completely different protein, HGF, much less SEQ ID NO:3.

Accordingly, Applicants submit that a combination of Stahl et al, Fuslang and Oliveras-Trejo et al would not result in the current invention.

Finally, as noted, Jet et al is directed to "recombination flounder growth hormone form Escherichia coli". The first 15 codons have been randomly mutagenized. As a result two genes encoding fGH have been identified. When compared to the original codon sequence it can be clearly seen that more than one codon is changed and that changes to optimal as well as rate codons occurred (emphasis added, fig. 3, page 187).

Thus, a person skilled in the art can conclude from the teaching of Jeh et al that for codon optimization i) more than one change of a codon is required and ii) that not only changes to optimal codons required by also changes to rare codons, i.e. a balance between optimal and rare codons must exist. Therefore, a combination of Stahl et al, Fsulang, Oliveras-Trejo and Jeh et al would not result in the current invention.

Accordingly, Applicants respectfully request that the 103(a) rejection be withdrawn and that Claims 1-6 as herein presented be placed into condition for allowance.

No further fee is required in connection the filing of this Amendment. If any additional fees are deemed necessary, authorization is given to charge the amount of any such fee to Deposit Account No. 08-2525.

Respectfully submitted,

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